DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control and Prevention

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Dear Colleague:

Today, the National Institutes of Health announced the results of the international iPrEx clinical trial, co-sponsored by the Bill and Melinda Gates Foundation, that examined whether a pill containing two drugs used to treat HIV can also help prevent HIV infection – an approach called pre-exposure prophylaxis, or PrEP. The trial found that daily oral use of tenofovir plus emtricitabine (brand named Truvada®) provided an average of 44 percent (95% CI 15 to 63%) additional protection to trial participants that included gay, bisexual, and other men who have sex with men (MSM), as well as transgendered women who have sex with men. These participants also received a comprehensive package of prevention services that included monthly HIV testing, condom provision, counseling, and management of other sexually transmitted infections.

A key finding of this trial was that the level of protection individuals received from PrEP was dependent on how consistently they used it. Among those whose data (based on self-reports, bottles dispensed, and pill counts) indicates use on 90 percent or more days, HIV risk was reduced by roughly 73 percent (95% CI 41 to 88%); while among those whose adherence by the same measure was less than 90 percent, HIV risk was reduced by only 21 percent (95% CI, from 52% reduction to a 31% increase). Risk behavior among participants declined overall during the trial both in terms of decreases in the number of sexual partners and increases in condom use, likely as a result of the intensive risk reduction counseling provided as part of the trial.

While these trial results represent a significant advance in HIV prevention research, it is not time for anyone to abandon condoms or other proven risk reduction strategies. The investigators found that PrEP was only partially effective, and, therefore, it cannot be seen as the first line of defense against HIV.

Given the severity of the HIV epidemic among MSM in the United States, another prevention tool with potential additive benefit is welcome news. Yet, additional research is needed to address the many real-world questions that remain to be answered, including feasibility, cost, and impact in non-trial settings. Success will depend on whether we can reach the MSM at highest risk for HIV and identify ways to achieve the high levels of drug adherence needed for maximum protection. It will also be critical that any use of PrEP take place in tandem with effective risk reduction counseling, condoms, and other tools needed to prevent increases in risk behavior which could offset the benefits of PrEP. The potential impact of PrEP on the U.S. epidemic will depend on how effectively we utilize it in combination with all available treatment and prevention strategies.

To help ensure the safe, effective, and appropriate use of PrEP in the United States, CDC will be developing guidelines for healthcare providers on the use of PrEP among MSM. CDC will fully

review the trial data and publish interim guidance in the coming weeks in the *Morbidity and Mortality Weekly Report,* to be followed in several months by formal U.S. Public Health Service guidelines. The agency urges individuals and their doctors to await those guidelines before use. However, Truvada® is widely available and frequently used for the treatment of persons with HIV infection, and CDC recognizes that some physicians may receive immediate inquiries from individuals at high risk for HIV who are interested in using PrEP. In this letter, we offer initial cautions and considerations to assist clinicians until more complete guidance is available. Based on the findings of the iPrEx study, any clinician considering administering Truvada® for HIV prevention before further guidance is issued should consider the following:

- Daily Truvada® was shown to be partially effective *when used in combination with HIV testing at regular intervals, condoms, and other proven prevention methods*. Therefore, PrEP should be considered a risk reduction strategy that can be *added* to existing strategies. In other words, other proven risk reduction strategies should not be abandoned.
- Truvada®, given prophylactically, has been shown effective for reducing HIV infection only among gay and bisexual men, and trangendered women who have sex with men. There are no data regarding its benefit among heterosexuals or injection drug users. Safety for adolescents, or MSM with significant renal, hepatic, or other serious chronic disease has not been studied.
- Truvada® (300 mg tenofovir disoproxil fumarate and 200 mg emtricitabine) taken once daily is the only drug regimen shown in a clinical trial to be safe and effective for PrEP in gay and bisexual men. Therefore, at this time, only this medication should be considered for PrEP. No other antiretroviral should be prescribed for PrEP because the safety and efficacy of other antiretroviral has not been established for long-term use by HIV-negative persons. Providers and patients should be aware that HIV prevention is not a labeled indication for the use of Truvada®.[i]
- Adherence is a critical factor and providers should give counseling and support to assist anyone prescribed PrEP in taking their medication daily. There are no data on the efficacy of other possible dosing schemes. Moreover, the iPrEx trial found that PrEP provided a high level of protection only to those who took the pills regularly; protection was very low among those who did not adhere to the daily regimen well.
- Any person being considered for PrEP should be explicitly informed of the potential benefits, side effects, costs, and unknown long-term risks for this approach. The costs associated with PrEP are anticipated to be significant if insurance coverage is not available.
- Anyone considering PrEP must first be tested for HIV to confirm they are not infected and evaluated for any health conditions that may be impacted by PrEP use. Before initiating PrEP, MSM must have:
    - A documented negative HIV test immediately before starting PrEP medication
    - Testing to exclude acute HIV infection if symptomatic
    - Documented normal renal function (calculated creatinine clearance is $\geq$ 60 ml/min)
    - Hepatitis serology to determine if they have active hepatitis B infection and immunization against hepatitis B if susceptible. While tenofovir and emtricitabine are used to treat active hepatitis B (and therefore are not contraindicated for PrEP), it should not be stopped without close observation of liver function

because of a small risk of flare resulting in serious liver damage without proper clinical management.
    - Screening and treatment for sexually transmitted infections
- While taking Truvada® for PrEP, all patients must be evaluated at frequent intervals (e.g., at least every 3 months) for:
    - Repeat HIV testing, before medication refills, to ensure that PrEP is stopped promptly if HIV infection has occurred
    - Assessments of medication adherence and HIV risk behaviors with appropriate levels of support, counseling, and referrals provided to address identified concerns
    - Assessment and management of medication side effects and toxicities (may be done as early as 1 month after initial PrEP prescription)
- On discontinuing Truvada® for PrEP, patients should have:
    - An HIV test to document infection status
    - Linkage to risk reduction support services as indicated
- If HIV seroconversion occurs while taking PrEP, patients must have:
    - Instruction to stop taking PrEP medication
    - Confirmatory tests for HIV infection, as well as viral load and genotypic resistance testing
    - Prompt linkage to ongoing HIV care
    - Assisted partner notification services

Research is underway around the world to determine efficacy of PrEP regimens in other populations, such as injection drug users and high-risk heterosexuals. Completing these trials is critical because PrEP regimens may not work the same way for all types of exposures, and different factors influence transmission through each route. Until those results are known, consideration of PrEP for HIV prevention in populations other than MSM is not recommended.

The best approach for the overall health of gay and bisexual men continues to be to provide comprehensive HIV prevention services and promote a combination of proven risk reduction strategies, including the correct and consistent use of condoms, HIV testing at regular intervals, knowledge of HIV status and the status of any partners, education to reduce drug use and sexual risk behavior, reduction in the number of sex partners, and testing and treatment of other sexually transmitted infections. PrEP should only be recommended in combination with these other proven approaches.

In addition to developing public health guidelines, CDC will be pursuing a range of activities to address key unanswered questions (such as how PrEP will work in real life settings) and promote the effective and strategic use of PrEP For additional information, please refer to the PrEP fact sheet: http://www.cdc.gov/nchhstp/newsroom/PrEPforHIVFactSheet.html. Updated information will be provided as it becomes available through e-mails and on our web site.

Sincerely,

/Kevin A. Fenton/

Kevin A. Fenton, M.D., Ph.D., F.F.P.H.
Director,
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

/Jonathan H. Mermin/

Jonathan H. Mermin, M.D., M.P.H.
Director,
Division of HIV/AIDS Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention

[i] These recommendations do not reflect current Food and Drug Administration-approved labeling for TDF/FTC.